

# CARDIOVASCULAR MEDICINE

## Interventricular and intra-left ventricular electromechanical delays in right ventricular paced patients with heart failure: implications for upgrading to biventricular stimulation

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**Objective:** To correlate, in patients with right ventricular pacing (RVP), the QRS width with electromechanical variables assessed by pulsed Doppler tissue imaging echocardiography. Secondly, to find reliable parameters for selecting RVP patients who would respond to biventricular pacing (BVP).

**Methods:** 26 randomly selected control patients with RVP (mean (SD) ejection fraction 74 (3)%) (group A) were matched on sex and age criteria with 16 RVP patients with drug resistant heart failure (mean (SD) ejection fraction 27 (5)%) (group B). All patients were pacemaker dependent and all underwent pulsed Doppler tissue imaging echocardiography. This technique provided the intra-left ventricular (LV) electromechanical delay and the interventricular electromechanical delay. The Gaussian curve properties of data from group A patients provided the normal range of ECG and echographic parameters.

**Design:** Prospective study.

**Setting:** University hospital (tertiary referral centre).

**Results:** Data from the control group showed that an interventricular electromechanical delay or an intra-LV electromechanical delay  $> 50$  ms would identify patients with a significantly abnormal ventricular mechanical asynchrony ( $p < 0.05$ ). In the same manner, a QRS width  $> 190$  ms was considered significantly larger in group B patients ( $p < 0.05$ ) than in controls. In Group B patients, there was no correlation between the QRS width and the interventricular electromechanical delay ( $r = -0.23$ , NS) or the intra-LV electromechanical delay ( $r = 0.19$ , NS). Seven group B patients (44%) were misclassified by ECG criteria for ventricular mechanical asynchrony identification: four patients (25%) had a QRS width similar to that of controls but with a significantly prolonged intra-LV electromechanical delay and interventricular electromechanical delay; and three patients (19%) had a QRS width significantly larger than that in controls but without significant ventricular mechanical asynchrony.

**Conclusions:** The QRS width is not a reliable tool to identify RVP patients with ventricular mechanical asynchrony. In RVP patients, an interventricular electromechanical delay or intra-LV electromechanical delay  $> 50$  ms reflects a significant ventricular mechanical asynchrony and should be required to select patients for upgrading to BVP.

Biventricular pacing (BVP) has recently been proposed as a new treatment option for patients with severe heart failure and large QRS width.<sup>1–4</sup> By providing early stimulation in the late activated segments, BVP improves systolic wall motion coordination and optimises left ventricular (LV) filling.<sup>5–7</sup> A QRS width above 200 ms has been arbitrarily required to upgrade right ventricular pacing (RVP) in patients with heart failure to BVP<sup>8–9</sup> because such a wide QRS has been suggested to correspond with notable inter- or intra-LV mechanical asynchrony.<sup>8–10</sup> However, the relation between electrical ventricular asynchrony (that is, the QRS duration) and the presence of objective mechanical ventricular asynchrony in RVP patients has never been clearly characterised. New echocardiographic techniques such as tissue Doppler imaging provide reproducible and non-invasive assessment of ventricular electromechanical parameters.<sup>5–7 11</sup>

The aim of the present study was to assess the potential relation between the QRS duration and the presence of interventricular or intra-LV asynchrony in RVP patients with drug resistant heart failure. Additionally, in the same patients, the correlation between a QRS duration  $> 200$  ms and the presence of interventricular or intra-LV asynchrony was assessed.

## METHODS

### Inclusion criteria

The patients had to meet the following criteria to be included in the study: apical RVP, complete atrioventricular block or His bundle ablation to consider only pacemaker dependent patients, pacemaker implanted for at least six months, and sinus rhythm with a resting heart rate between 60–65 beats/min. Two groups of patients were considered in the present study. Group A patients (controls) were strictly asymptomatic, without echocardiographic structural cardiac disease or history of ischaemic or primitive cardiomyopathy. These control patients were matched by sex and age with group B patients (see below) and consecutively included in the study. Group B (studied population) patients had ischaemic or idiopathic dilated cardiomyopathy, New York Heart Association (NYHA) functional class III or IV despite maximum tolerated medical treatment (angiotensin converting enzyme inhibitors,  $\beta$  blockers, diuretics, spironolactone), and LV dysfunction (ejection fraction  $< 35\%$ ).

**Abbreviations:** BVP, biventricular pacing; LV, left ventricle; NYHA, New York Heart Association; RVP, right ventricular pacing

## Study protocol

Both patient group underwent the same protocol. The longest QRS duration was measured on a 12 lead surface ECG recorded at a speed of 50 mm/s. The pacemaker was programmed to DDD mode and the atrioventricular delay was adjusted in every patient. According to Ritter and colleagues,<sup>12</sup> the atrioventricular delay that provided the longest filling time without truncation of the A wave by means of pulsed Doppler analysis of the transmitral flow was chosen. The first part of the echocardiographic study was a conventional examination (Sequoia, Acuson Inc, Mountain View, California, USA). Five consecutive beats were averaged. Mitral Doppler flow was recorded to measure both E and A wave maximal velocities and the total diastolic filling time. The aortic and pulmonary ejection flows were measured respectively in the four chamber apical and parasternal views. The aortic pre-ejection time interval was defined as the time duration between the stimulation spike on the surface ECG and the onset of the aortic ejection flow, whereas the pulmonary pre-ejection time interval was defined as the time duration between the stimulation spike on the surface ECG and the onset of the pulmonary ejection flow. Tissue Doppler imaging was performed in the pulsed Doppler mode. Acoustic power, gain, dynamic range, and filters were set for each myocardial area analysed once the optimal atrioventricular delay was determined and programmed. The explored areas were respectively the basal LV septum, free wall, and inferior and anterior walls. The LV wall electromechanical delays (defined as the time duration between the stimulation spike on the surface ECG and the onset of the S wave corresponding to the systolic motion of a given LV wall obtained by the tissue Doppler imaging technique) (fig 1) were quantified and compared between group A and B patients.<sup>7–11</sup> The intra-LV electromechanical delay was calculated as the time difference between the shortest and the longest LV wall electromechanical delays (fig 1) whereas the interventricular electromechanical delay was the time difference between the aortic and pulmonary pre-ejection time intervals.

## Statistical analysis

Group A patients (control group) were included in the study to characterise the range of the intra-LV and interventricular

electromechanical delays in the population of RVP patients with a normal cardiac function. This was defined as the following: the statistical  $\alpha$  risk was fixed at 0.05 so that the physiological range of the parameters would be included in the mean (2 SD) range, which accounts for 95% of the control group distribution.<sup>13</sup> The international statistical consensus requires a sample size of at least 25 subjects for using these specific Gaussian curve properties.<sup>13</sup> Consequently, the upper limit for a statistically normal value of intra-LV and interventricular electromechanical delays was the respective mean (2 SD) value. Any value above this limit in group B patients was considered significantly different from the control group and, accordingly, the patient was classified as presenting with an interventricular or intra-LV significant asynchrony compared with the control population.

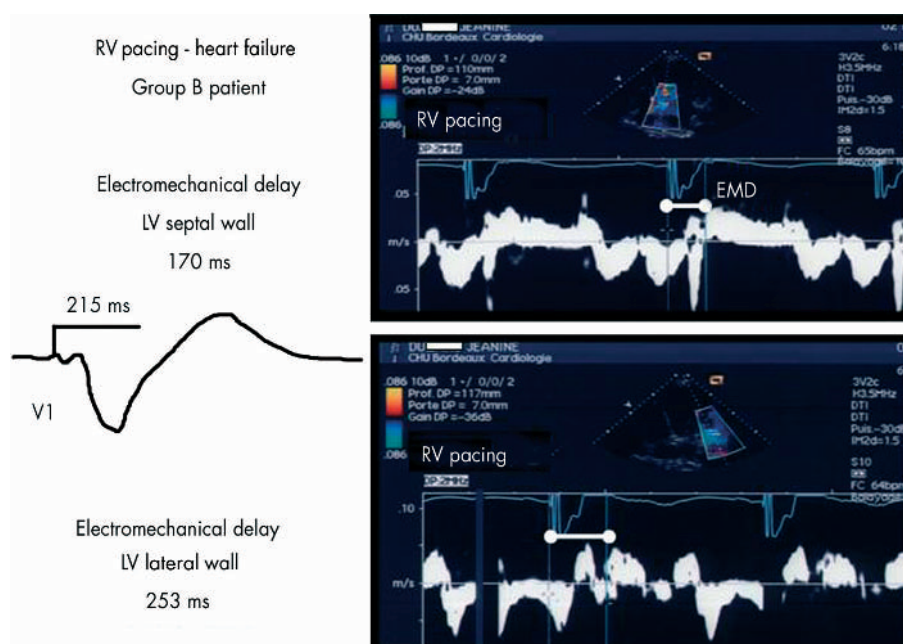
The intraobserver correlations for intra-LV and interventricular electromechanical delay calculation were, respectively, 0.93 and 0.95, and the interobserver correlations were, respectively, 0.89 and 0.93 in a sample size of 15 patients.

Differences between patient groups were assessed by using Student's *t* test for quantitative variables and Fisher's test of exact probability for qualitative variables. Correlations between quantitative variables were determined by Pearson's correlation coefficient. A probability value of  $p < 0.05$  was considered significant. All data are presented as mean (SD) or percentages.

## RESULTS

### Study population

Forty two patients participated in the study. Twenty six consecutive patients (18 men, mean (SD) age 68 (12) years) constituted group A (control group). By definition, they were strictly asymptomatic. The mean LV ejection fraction was relatively high at 74 (3)%. Nineteen patients (73%) were His ablated for brady-tachy syndrome and seven (27%) had pacemakers implanted for complete atrioventricular block. There was no significant difference between the two groups in terms of sex, age, and pacemaker indication (table 1). Sixteen patients (14 men, mean (SD) age 63 (11)) constituted group B. The mean LV ejection fraction was 27 (5)%. Nine patients had an ischaemic cardiomyopathy and seven an idiopathic cardiomyopathy (table 1). The mean QRS



**Figure 1** The top panel shows, in a patient with sinus rhythm and apical right ventricular complete capture, the value of the shortest electromechanical delay (EMD) calculated for the septal left ventricular (LV) wall (170 ms). The QRS duration reaches 215 ms. The EMD was defined in this example by the interval between the stimulation spike and the onset of the S wave corresponding to the systolic motion of the septal LV wall. The bottom panel shows the longest EMD for the lateral LV wall (253 ms), showing highly heterogeneous systolic LV dynamics and an intra-LV asynchrony reaching 83 ms (range [253–170]).

**Table 1** Patients characteristics

Variables	Controls (group A) (n = 26)	Heart failure (group B) (n = 16)	p Value
Age (years)	68 (12)	69 (11)	NS
Women	8 (31%)	12.5%	0.05
LV ejection fraction (%)	74 (3)	27 (5)	<0.001
QRS width (ms)	156 (11)	210 (20)	<0.001

Data are mean (SD). LV, left ventricular.

width before pacemaker implantation in group B patients was 142 (23) ms versus 89 (8) ms in group A ( $p < 0.01$ ). Eleven patients (68%) received a pacemaker for brady-tachy syndrome followed by His bundle ablation and five (32%) for complete atrioventricular block. The mean paced QRS width was 156 (11) ms in group A versus 210 (20) ms in group B ( $p < 0.01$ ) (table 1). Twelve patients (75%) in group B and none in group A had a QRS duration  $> 200$  ms ( $p < 0.01$ ). Ten group B patients were in NYHA functional class III and six in class IV after at least six months of RV pacing.

### Echocardiographic data

#### Control group: group A

In patients without cardiomyopathy, the mean aortic pre-ejection time interval was 150 (22) ms and the mean pulmonary pre-ejection time interval was 117 (22) ms. These measurements resulted in a mean interventricular electromechanical delay reaching 32 (10) ms and a mean intra-LV electromechanical delay of 33 (9) ms. Accordingly (see Statistical analysis section), all group B patients with a value above 50 ms (mean (2 SD) of control patients) were considered to present with a significantly abnormal interventricular or intra-LV asynchrony. All control patients presented with a value of interventricular and intra-LV electromechanical delay  $< 50$  ms. No significant correlation was found between the QRS width and the interventricular electromechanical delay ( $r = 0.20$ , NS) or the intra-LV electromechanical delay ( $r = 0.06$ , NS). There was a significant correlation between the aortic pre-ejection time interval and the interventricular delay ( $r = 0.48$ ,  $p = 0.03$ ) but not the intra-LV delay ( $r = 0.26$ , NS).

#### Patients with heart failure: group B

Table 2 summarises the echocardiographic data. In patients with severe heart failure, the mean aortic pre-ejection time interval was 208 (23) ms ( $p < 0.01$  compared with group A). No significant correlation was observed between the QRS width and the aortic pre-ejection time interval ( $r = 0.12$ , NS). The mean pulmonary pre-ejection time interval was 162 (33) ms ( $p < 0.01$  compared with group A) without significant correlation with the QRS width ( $r = 0.18$ , NS). The mean interventricular delay was 55 (14) ms ( $p < 0.01$  versus group A); no significant correlation was found with the QRS width ( $r = -0.23$ , NS) (fig 2, left panel). The mean intra-LV electromechanical delay was 52 (13) ms ( $p < 0.01$  compared

with group A) without significant correlation with the QRS duration ( $r = 0.19$ , NS) (fig 2, right panel). There was a significant but poor correlation between the aortic pre-ejection time interval and the interventricular delay ( $r = 0.33$ ,  $p = 0.05$ ). The correlation between the aortic pre-ejection time interval and the intraventricular delay was also significant but poor ( $r = 0.49$ ,  $p = 0.04$ ). Four patients in group B had a QRS duration  $< 200$  ms and all of them presented with an intra-LV or interventricular asynchrony ( $> 50$  ms) (fig 2). In the 12 remaining group B patients who had a QRS duration  $> 200$  ms, three exhibited neither interventricular nor intra-LV asynchrony compared with control patients (fig 2). No significant difference was observed between patients with ischaemic and those with primitive cardiomyopathy in terms of LV ejection fraction, QRS width, aortic and pulmonary pre-ejection time interval, and interventricular electromechanical delay. In contrast, the intra-LV electromechanical delay was significantly longer ( $p < 0.05$ ) in patients with ischaemic cardiomyopathy. The first activated LV wall was the septal one in 75% of group B patients and in 81% in controls (NS), the anterior wall in 19%  $v$  12% (NS), and the inferior wall in 6%  $v$  7%, respectively (NS). The most delayed LV wall was the free wall in 56% of group B patients and in 84% of controls ( $p < 0.05$ ), the anterior wall in 12%  $v$  4% ( $p < 0.05$ ), and the inferior wall in 32%  $v$  12% ( $p < 0.05$ ), respectively (table 3).

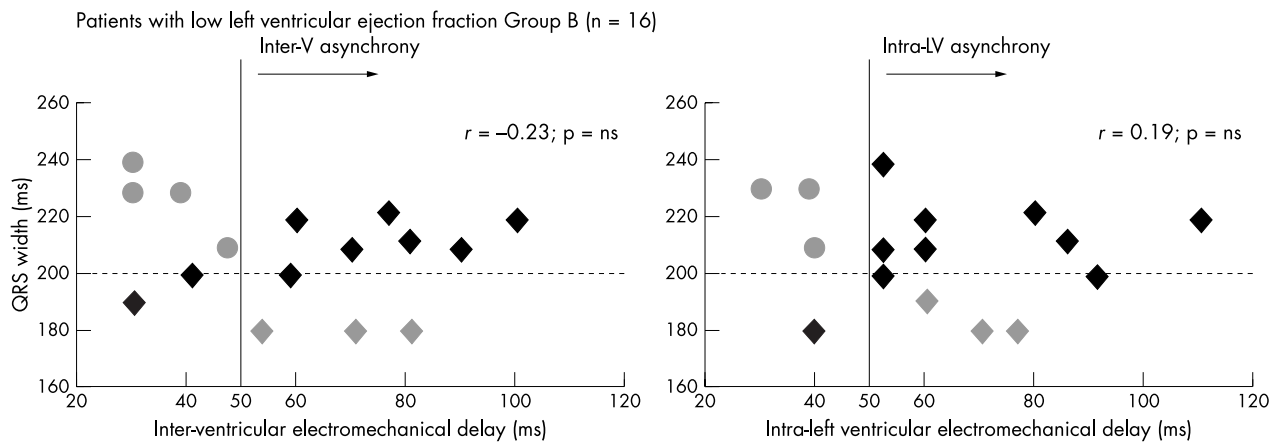
### DISCUSSION

The present study assessed the regional qualitative and quantitative tissue Doppler imaging patterns caused by RVP in patients with and without heart failure. These patterns were graduated in a time scale so that the degree of intra-LV and interventricular electromechanical asynchrony could be defined. Data from the control population permitted us to determine the normal range of RVP induced ventricular asynchrony from which abnormal asynchrony could be identified in the group with heart failure. It is theoretically conceivable that differences in ventricular asynchrony between patients with heart failure and controls may not be caused entirely by heart structural abnormalities. Indeed, 75% of our patients with heart failure (versus none in the control group) were taking  $\beta$  blockers, which may potentially worsen ventricular conduction disturbances. However, the aim of the study was to identify patients with pacemaker dependent heart failure who, despite optimal pharmacologi-

**Table 2** Echocardiographic Doppler data

Variables	Controls (group A) (n = 26)	Heart failure (group B) (n = 16)	p Value
Aortic pre-ejection time interval (ms)	150 (22)	208 (23)	<0.001
Pulmonary pre-ejection time interval (ms)	117 (22)	162 (33)	<0.001
Interventricular delay (ms)	32 (10)	55 (14)	<0.001
Intra-LV delay (ms)	33 (9)	52 (13)	<0.001

Data are mean (SD).



**Figure 2** Left: Distribution of interventricular EMDs according to the QRS width in group B patients. There was no significant correlation between these two variables. An abnormally increased interventricular asynchrony ( $> 50$  ms) was found in 63% of group B patients. Three patients with a QRS width  $< 200$  ms were found to have an abnormally increased interventricular asynchrony (grey diamonds) whereas four patients had a QRS width  $> 200$  ms but without interventricular asynchrony (grey circles). Right: Distribution of intra-left ventricular (LV) electromechanical delays according to QRS width. There was no significant correlation between these two variables. An abnormally increased intra-LV asynchrony ( $> 50$  ms) was found in 75% of the patients. Three patients with a QRS width  $< 200$  ms were found to have an abnormally increased intra-LV asynchrony (grey diamonds) whereas three patients had a QRS width  $> 200$  ms but without interventricular or intra-LV asynchrony (grey circles).

**Table 3** LV walls with the shortest and the longest electromechanical delays (EMD) in group A and B patients

	Septal LV wall		Anterior LV wall		Inferior LV wall		Lateral LV wall	
	A	B	A	B	A	B	A	B
LV wall with the shortest EMD % (n)	81% (21)	75% (12)	12% (3)	19% (3)	07% (2)	06% (1)	0	0
LV wall with the longest EMD % (n)	0	0	04% (1)	12%* (2)	12% (3)	32%* (5)	84% (22)	56%* (5)

\* $p < 0.05$ .

cal treatment, present with pathological mechanical ventricular asynchrony.

This new way of considering heart failure in paced patients provided useful insights. Firstly, in RVP patients, there is no correlation between electrical features (QRS width) and the degree of electromechanical ventricular asynchrony. Secondly, independent of the presence of heart failure, the last activated LV wall was not always the free wall and the first one activated was not always the septal wall, as has already been shown in patients with spontaneous atrioventricular conduction.<sup>5-7, 14</sup> Thirdly, in group B more patients had an RVP induced intra-LV than an interventricular asynchrony, suggesting that in these patients the major cause of LV function impairment is likely to be the presence of intra-LV asynchrony. As BVP results in the improvement of intra-LV rather than of interventricular synchrony,<sup>5-7</sup> RVP patients who present with an abnormally increased intra-LV asynchrony should benefit from BVP upgrading. Since our data did not show any significant correlation between the degree of intra-LV asynchrony and the QRS width, considering the lower limit of 200 ms of QRS width to be a criterion for upgrading patients from RVP to BVP may not be justified. Indeed, whereas four patients with heart failure (25% of group B) had a QRS width below 200 ms, they all presented with abnormal interventricular or intra-LV asynchrony and should be upgraded to BVP. In contrast, three patients (19% of group B) had a QRS width above 200 ms but had no abnormal ventricular asynchrony compared with the controls and may not be good candidates for BVP despite the large QRS width. In patients with heart failure with a large QRS width, multicentre randomised studies found that about 20%

were non-responders even though all the included patients had a wide QRS.<sup>1-3</sup> These non-responders may have presented with no important mechanical LV asynchrony despite the large QRS width.

### Limitations of the study

The sample size of patients with heart failure was relatively small because these patients had to fit strict inclusion criteria: NYHA functional class III or IV, LV ejection fraction  $< 35\%$ , sinus rhythm, and a resting heart rate comparable with that of controls. Furthermore, they had to be pacemaker dependent and to have been paced for more than six months.

We used the tissue Doppler imaging technique to quantify the degree of ventricular mechanical asynchrony. Even though this technique has been intensively studied in clinical research,<sup>5-6, 11, 14-16</sup> it is not yet widely used clinically, which limits the application of the method.

### Conclusion

The QRS width does not seem to be a good parameter of conduction disturbances or a reliable identifier of paced patients with heart failure likely to benefit from BVP. The need for alternative methods such as new echocardiographic techniques may be required. However, further studies with larger populations are needed to confirm these data.

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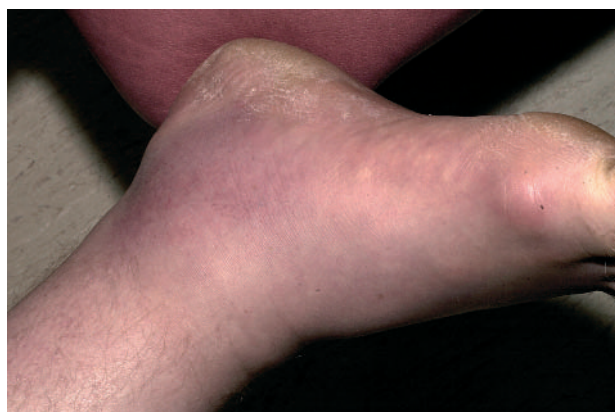
## IMAGES IN CARDIOLOGY

## A case of rheumatic fever

A 50 year old man presented with painful swelling in his feet, knees and right wrist 14 days after a throat infection (below). An ECG at the onset of symptoms had shown first degree heart block (ECG 1). His ESR was 108 mm/hr, CRP 336 mg/ml, WBC at  $14.3 \times 10^9/l$ . ECG was normal (ECG 2). Treatment was started with ciprofloxacin, clarithromycin (he is penicillin sensitive) and tinzaparin for presumed cellulitis.

He developed chest pain and became pyrexial (38.5 °C). ECG showed saddle shaped ST elevation in the anterior chest leads (ECG 3). Creatinine kinase was 19 and 20 iu/l (25–175), possibly low because of inactivation by low tissue glutathione (convalescent creatinine kinase was 114 iu/l). Troponin T was <0.01 µg/ml (<0.1). He was treated with aspirin 300 mg and pain relief. Echocardiogram was normal. Chest pain persisted and he went into atrial fibrillation (ECG 4); anticoagulation was initiated. Antistreptolysin O titres were raised at >800units/ml (<200), anti DNase B 3840 units/ml (<240) and these subsequently fell indicating evidence of recent group A streptococcus infection. Throat swab showed scanty candida only.

At outpatient review he was in sinus rhythm (ECG 5) and there were no audible murmurs. He was commenced on clarithromycin 250 mg twice daily as prophylaxis and the warfarin was stopped.



As doctors in the UK are persuaded not to prescribe antibiotics for viral sore throats this will inevitably mean that more group A streptococcal throat infections go untreated. Can we expect to see a resurgence of rheumatic fever, a condition that many doctors trained in the developed world will never have seen, or will other host and organism related factors keep it at bay?

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